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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,500	01/26/2004	Brett P. Monia	ISPH-0825	2967

7590 08/23/2006

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/765,500	MONIA ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/26/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,077,672. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of each application embrace and overlap each other. For example, the oligonucleotides of the patented claim 3 are up to 30 nucleotides in length comprising at least an eight nucleotide portion of recited SEQ ID NOS and the invention of the instant claim 3 is drawn to oligonucleotides that are 8-30 nucleobases in length that comprise the same recited SEQ ID NOS. The claim 3 of the instant application anticipates the invention of the patent. The instant claim 1 is drawn to antisense oligonucleotides 8-30 nucleobases in length targeted to a TRADD encoding nucleic acid and claim 1 of the patent is drawn to antisense oligonucleotides targeted to the 3' UTR

of a TRADD encoding nucleic. The claim 1 of the patent anticipates the invention of the instant application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 5-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goeddel [US 5,563,039] in view of Baracchini et al [US 5,801,154].

The instant invention is drawn to antisense oligonucleotides targeted to a nucleic acid encoding a human TRADD and methods of inhibiting expression of the TRADD where the oligonucleotides can contain modifications as recited in the instant claims.

Goeddel et al teach nucleic acids encoding TRADD and also teach the use of antisense oligonucleotides targeted to a TRADD encoding nucleic acid for its inhibition

(see column 5). It has been taught to inhibit TRADD when one desires to reduce TNF responsiveness, for example. Goeddel et al do not teach antisense that are specifically within the range of 8-30 nucleobases in length and do not teach the specific modifications recited in the instant claims.

Baracchini et al have taught at column 6, for example, that antisense oligonucleotides can be used for research purposes and have also taught at column 6 that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

It would have been obvious to modify the antisense molecules disclosed by Goeddel et al as taught by Baracchini et al since Baracchini et al have taught the benefits of making antisense with various modifications and have also taught the

preferred size of antisense oligonucleotides. One would want to make such modifications in order to make the antisense oligonucleotides more stable against nucleases and to make antisense oligonucleotides bind more tightly to its target, for example.

The invention as a whole would therefore have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of TRADD in cells in culture, does not reasonably provide enablement for methods of treating disease via TRADD targeted antisense oligonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant invention is drawn to the inhibition of TRADD in an animal for treating or preventing disease via the administration of antisense oligonucleotides targeting a TRADD encoding nucleic acid.

The instant specification asserts that it is believed that a number of disease states and/or disorders are a result of either aberrant activation or functional mutations in the molecular components of signal transduction pathways and then assert that "consequently, considerable attention has been devoted to the characterization of these proteins" (pages 1 and 2). The specification then describes the association of TNF with various disease states or conditions (page 2). The instant specification then asserts that TRADD is a downstream effector protein of TNF action and would serve as an effeicient target for disease treatment or prevention (page 3). The specification discloses the inhibition of TRADD in cells in culture.

There is no disclosure of any phenotype or effect on cells that have been treated with TRADD antisense such that a correlation to treating disease can be made. The specification does not disclose any particular disease or condition that can be treated or prevented with the inhibition of TRADD via antisense oligonucleotides. The specification, therefore fails to provide any particular disease or condition that one would know can be treated with antisense targeted to TRADD. One would need to perform undue trial and error experimentation to determine what diseases that may be associated with TNF might be treatable or preventable via the inhibition of a downstream effector TRADD via antisense inhibition.

Furthermore the state of the art in the art of antisense based therapy was unpredictable at the time of invention. Jen et al [STEM CELLS Vol. 18:307-319, 2000] Disscuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances

made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using

lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is nt clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

For one to practice the full scope of the claimed invention one of skill in the art would be required to perform undue trial and error experimentation. The experimentation would include the determination of just what diseases could be treated or prevented via TRADD expression inhibition and also experimentation to overcome the obstacles described in the above references, for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635